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PRINCIPAL INVESTIGATOR: Terry Goldberg, PhD

CONTRACTING ORGANIZATION: The Feinstein Institute for Medical Research
Manhasset, NY 11030

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6. AUTHOR(S)
Terry E. Goldberg, PhD

E-Mail: tgoldber@nshs.edu

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The Feinstein Institute for Medical Research
350 Community Drive
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14. ABSTRACT

As the Alzheimer's disease field moves to studies and intervention trials in the preclinical phase and early prodromal period, it will be necessary to measure everyday function in an increasingly more sensitive and sophisticated way to capture more subtle impairments. One approach to increasing sensitivity in functional measures is to use performance based instruments, such as the UCSD Performance-based Skills Assessment (UPSA), in Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD) research. In this test patients are observed and their response scored as they actually perform proxies for real world tasks and it contrasts with more typical informant based measures. In a preliminary study we compared patients with MCI, patients with mild AD, and healthy age matched controls on the UPSA. We found that patients with MCI had compromises in everyday functional competence and that the UPSA was strikingly sensitive to these (Goldberg et al, 2010). *However, that study was not longitudinal.* Therefore, it is important that we obtain data on the longitudinal characteristics of the UPSA. Over the past year we have enrolled 25 subjects into our protocol. Of these 24 received the six week follow up. Another 26 subjects received the one year follow up. Our total number of enrolled subjects is 48. Preliminary results demonstrated 1. highly significant differences between the diagnostic groups (healthy control (HC), Mild Cognitive Impairment (MCI), AD) such that the HC group outperformed the patient groups; 2. Robust relationship between the short and long forms for the UPSA; and 3. a pattern of longitudinal stability in the HC group and decline in the AD group. This set of results is in keeping with our predictions.

15. SUBJECT TERMS
Alzheimer's disease, Mild Cognitive Impairment, functional impairment, UPSA

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Introduction

As the Alzheimer's disease field moves to studies and intervention trials, it will be necessary to measure everyday function in an increasingly more sensitive and sophisticated way to capture more subtle impairments. One approach to increasing sensitivity in functional measures is to use performance based instruments, such as the UCSD Performance-based Skills Assessment (UPSA), in Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD) research. In this test patients are observed and their response scored as they actually perform proxies for real world tasks (such as determining which bus route to take, writing a check, planning a trip to the beach, and recalling an appointment's time and place). In a preliminary study we compared patients with MCI, patients with mild AD who by diagnosis have functional impairments, and healthy age matched controls on the UPSA, as well as measures of cognition (e.g., episodic memory, semantic memory, executive function, speed). We found that patients with MCI had compromises in everyday functional competence and that the UPSA was strikingly sensitive to these (Goldberg et al, 2010). *However, that study was not longitudinal.* Therefore, it is important that we obtain data on the longitudinal characteristics of the UPSA in these populations, including the severity of decline in this measure over time, the relationship of decline to cognitive changes in order to determine the validity of the UPSA, and its technical psychometric characteristics (e.g., test-retest reliability). We will longitudinally assess magnitude of decline in the UPSA individuals with MCI and mild AD assessed at baseline, 6 weeks, and 12 months. We will compare and contrast decline in the UPSA with a commonly used measure of function administered to informants (the FAQ) in MCI and AD using Effect Sizes (ES) and mixed model repeated measures. We will determine the cognitive measures that best predict decline in the UPSA. We predict that the UPSA will decline over time in the MCI and AD groups with and demonstrate strong relationships to cognitive decline

Key Research Accomplishments

- We enrolled 25 new subjects into our protocol, including 17 HCs and 4 AD and 4 MCI subjects.
- Additionally 50 follow ups were conducted (26 of which were at one year). Thus, a total of 75 assessments was conducted.
- We have conducted all key preliminary analyses on our data, including mixed model repeated measures, effect sizes, and test retest reliability both for the UPSA long form and the short form.

Body

Mild Cognitive Impairment (MCI), a relatively newly defined diagnostic entity, is usually considered to be a possible transitional stage between CNS health and Alzheimer's disease (AD); it is thought to be an important locus for intervention, since both cognitive impairment and neuropathology are relatively circumscribed and thus may be more easily modified or arrested. As the field moves to studies and intervention trials, it will be necessary to measure function in an increasingly more sensitive and sophisticated way to capture more subtle impairments and to appreciate psychometric properties that may improve such sensitivity, including lack of ceiling effects or informant mediated biases. In individuals with amnesic MCI, the most widely used criteria (proposed by Petersen) require that functional ability be preserved, yet memory impairment must be at least 1.5 SD below the mean of a control group. Since cognitive impairment has been an important predictor of functional outcome in a wide variety of neuropsychiatric disorders, including traumatic brain injury, epilepsy, schizophrenia, stroke, and AD, there appears to be a paradox. One explanation for this discrepancy might be that the measures commonly used to rate function were designed to assess disability in various stages of AD and so weighted to very simple Activities of Daily Living (ADL) skills, which can be intact in MCI. Thus, it may be the case that if more sensitive measures were used, function would indeed be found to be compromised. An approach to increasing sensitivity in functional measures is to use performance based instruments, such as the UCSD Performance-based Skills Assessment (UPSA), not hitherto applied in MCI or AD research. In this test patients are observed and their response scored as they actually perform proxies for real world tasks (e.g., such as determining which bus route to take, writing a check, planning a trip to the beach, and recalling an

appointment's time and place). In a preliminary study, we compared patients with MCI, patients with mild AD who by diagnosis have functional impairments, and healthy age matched controls on the UPSA, as well as measures of cognition (e.g., episodic memory, semantic memory, executive function, speed). Consistent with our hypothesis, we found that patients with MCI had compromises in everyday functional competence and that the UPSA was strikingly sensitive to these (Goldberg et al, 2010). *However, that study was not longitudinal.* Therefore, it is key that we obtain data on the longitudinal characteristics of the UPSA in these populations, including test-retest reliability and magnitude of decline, and the relationship of decline to cognitive changes in order to determine the validity of the UPSA.

Aim 1. We will longitudinally assess magnitude of decline in the UPSA individuals with MCI and mild AD assessed at baseline, 6 weeks, and 12 months. We will compare and contrast decline in the UPSA with FAQ in MCI and AD using Effect Sizes (ES) and mixed model repeated measures. We will determine the cognitive measures that best predict decline in the UPSA using regression models. In an exploratory analysis we will assess reliable decline at the level of individual cases using RCI statistics. We predict that the UPSA will decline over time in the MCI and AD groups with ESs in the medium to large range and demonstrate robust relationships to cognitive decline.
Aim 2. We will determine the psychometric properties of the UPSA, including test-retest reliability (baseline-6 weeks) in MCI, as well as the HC and AD groups. Critically, we will examine the possibility of ceiling effects in the MCI and HC groups for various measures, and possible floor effects in the AD group. We will also assess kurtosis, skewness, and coefficient of variation. We predict that the UPSA will exhibit excellent psychometric properties.
Aim 3. We will assess the utility of a short form of the UPSA consisting of the Comprehension/Planning and Communication subtests that was developed by us in a prior study in each of the above contexts.

Subject Recruitment
Recruitment has been maintained. Recruitment began September 21, 2012 with North Shore-LIJ IRB and ORP approval. In the approximately 18 months since, we have recruited 48 subjects.

We enrolled 25 subjects in the one year period. Four other subjects were screen failures. Impressively nearly all these subjects underwent 6 week re-assessment. Furthermore 24 subjects had one year follow ups, suggesting a robust retention rate.

Enhanced recruitment of MCI and AD subjects will be emphasized. This will now be addressed in weekly recruiting meetings

Preliminary Data Analyses
Using a mixed model repeated measures analysis, we found that there was an overall group difference (F=, p=.0001). At baseline the effect size difference between the HC group and the MCI group was large (d=.63) and the effect size difference between the HC group and AD group was very large (d>2.0). The longitudinal (i.e., time) effect was non-significant (p=.13), though a trend for decline in the AD group was evident. (Please see Figures 1 and 2). Psychometrically, test-retest reliability from baseline to week 6 was robust in the group (.88). The short form was strongly related to long form performance, as the r was .97, thus suggesting that .94 variance was shared.

Reportable Outcomes
The N is now large and includes multiple longitudinal assessments for subjects. It will be prepared as an abstract for presentation.

Conclusion
Recruitment is proceeding. Subjects are being maintained in this longitudinal protocol; thus, rates of attrition are relatively low. Preliminary results ranging from psychometrics to validity are highly encouraging. Results are generally consistent with our hypotheses.

References

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Supporting Data

Figure 1

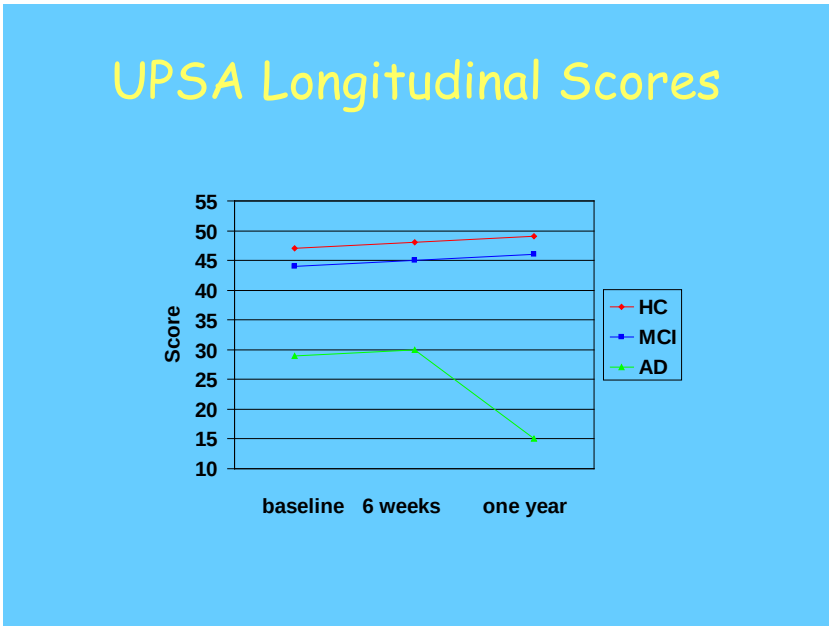

Figure 2